DESIGN DEVELOPMENT AND *IN-VITRO* CHARACTARIZATION BUCCAL PATCHES OF CETYLPYRIDINIUM CHLORIDE

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ABSTRACT

In present study buccal drug delivery of cetylpyridinium was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of buccal patches was developed by using polymers Eudragit-L100, HPMC K4M and HPMC K15M. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F12, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be within the pharmacopeial limits, *in vitro* drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours and compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

KEYWORDS

Cetyl pyridinium, Buccal patches, Polymers and Mucoadhesive.

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INTRODUCTION

In novel drug delivery systems, for periodontal disease, bacterial and fungal infection, various routes of administration tried. In comparison with other devices past from several years mucoadhesion has become very popular for the site of action e.g. buccal patch[1] offer greater flexibility and retains gastrointestinal tract or systemic delivery systems.

However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein by passing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients[2,3] that mildly and reversibly damage or irritate the mucosa, painless administration[4,5], easy withdrawal, facility to include permeation enhancer/enzyme competitive inhibitor or pH modifier in the drug formulation, versatility in the drug designing as multidirectional or unidirectional drug release system for local or systemic action[6-9]. The increasing necessity to deliver active medication to the patients efficiently with minimal side effects as well as improved compliance has accelerated the pace of invention of new drug delivery system[10-13]. Revolutionary drug delivery technology is extended to buccal route apart from oral[14-17]. The ability to increase the buccal permeation can be a valuable aid when oral administration of drug[18-21] is associated with problems. Though cetylpyridinium is best suitable for the treatment of gastro intestinal disorders through oral administration, it has some limitations such as it requires administration of high dose frequently due to its poor intestinal absorption (30-35%), elimination half life (5 hours) and adverse effects like allergic reactions, arrhythmia, cardio respiratory arrest, tachycardia, Headache[22]. Hence there is a need to modify the route of administration for better absorption of the drug[23-26]. The buccal route of administration may be better suited as it has many advantages over conventional oral route[27-29], and enhance patient compliance. Buccal penetration of Cetylpyridinium cannot be increased by niosomes or liposomes because of its size and rigid character of lipid layer. Hence there is a need for preparation of Cetylpyridinium patch for enhanced penetration through the buccal cavity, thereby reducing dose, minimizing frequency of administration and adverse affects, hence resulting in better patient compliance.

MATERIAL
Cetylpyridinium, Ethanol, Eudragit L-100, HPMC K15M, HPMC K4M, Methanol, Digital weighing balance, Digital pH meter, cyber pH-14L, Franz diffusion cell, Friability tester, Glassware, Hardness tester, UV-Visible Spectrophotometer.

METHODOLOGY
Determination OF UV Absorption maxima
Cetylpyridinium solution was prepared in 0.1 N HCl and diluted suitably. The UV spectrum of the solution exhibited absorbance maxima at 271 nm was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The procedure was repeated with pH 6.8 phosphate buffer.
Preparation of Standard Calibration Curve of Cetylpyridinium:
100 mg of Cetylpyridinium was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare the standard stock solution. This standard 10 ml of stock solution is diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100μg/ml (working standard). Then 0.2,0.4,0.6.0.8, and 1 ml of the working standard solution was taken in to the 10 ml standard measuring volumetric flask and made up to the volume with 0.1N HCl to prepare 2μg,4μg,6μg,8μg, and 10μg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 271 nm against 0.1 N HCl (pH 1.2) as blank. The procedure was repeated with pH 6.8 phosphate buffer and absorbance's were measured at 271 nm. The absorbance values given in Table No.2 and Figure No.1.
Selection of drug and other ingredients
1. Cetylpyridinium was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Buccal drug delivery system.

2. Eudragit-L100(mg), HPMC K4M(mg), HPMC $K_{15}M$(mg) were selected as matrix forming polymers.
3. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer.

FORMULATION
Development of Buccal patches
Buccal drug delivery patches were prepared by solvent casting method and formulation given in Table No.1.

Solvent casting method
Eudragit L100, HPMC K4M and HPMC K15M were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer. Cetylpyridinium (36mg), Propylene glycol and Tween 80 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of the solvent was monitored and controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccators.

EVALUATION OF BUCCAL PATCH BY PHYSICAL METHODS
Physical appearance
All the Buccal patches were visually inspected for color, clarity, flexibility and smoothness.

Thickness
This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.

Weight variation
The three disks of 2x2 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Flatness
Longitudinal strips were cut out from each buccal patches, one of the centre and two from either each side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.

Folding endurance
The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken.

Moisture uptake
The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84 % RH. After 3 days the films were removed and weighed the moisture percentage absorption of the buccal patch was found by the following formula.

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture content
The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ℃ for one day. The buccalpatches were reweighed until to get a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.

Swelling study
Completely dried membranes with a specified area (3.83 cm^2) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75 %(containing saturated solution of sodium chloride) in desiccators. Weight was taken until a constant weight was obtained on a single pan balance periodically. The swelling capacity (in weight %) of the membranes was calculated in terms of percentage increase in weight

of membrane over the initial weight of the specimen. The experiments were performed in three times and the average values were taken, for the calculation. The percentage degree of swelling (DS) was calculated as

$$DS (\%) = Ws-Wd/Wd \times 100$$

Where, W_s and W_d indicate the weight of the swollen and dry membranes average values respectively.

Drug content determination

The patch of area 3.83 cm^2 was cut and dissolved in PBS pH 7.4. Then to make polymer soluble, solvent dichloromethane and ethanol, were added and the volume was made up with PBS pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 271 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated. The results displayed in Table No.3.

EVALUATION OF BUCCAL PATCH BY PERMEATION STUDIES

Diffusion cell

Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried.

The total area of the receptor compartment that is exposed to the buccal patch for diffusion is 3.83 cm^2.

In vitro permeation studies using dialysis membrane

In vitro permeation of Cetylpyridinium from buccal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a buccal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 7.4 and the setup was placed over a magnetic stirrer with maintained at 37^{0}C room temperature. The samples of 3 ml had withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Cetylpyridinium in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 271 nm. The results displayed in Table No.4 and Figure No.2.

Kinetic modeling of drug release

Mechanism of drug release

Various models were tested for explaining the kinetics of drug release. In order to analyze the mechanism of the cetylpyridinium drug release, rate kinetics of the dosage form, this obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. The results displayed in Table No.5 and Figure No.3a, 3b, 3c and 3d.

Zero order release model

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$Q= K_0 t$$

Where, Q= amount of drug released at time t

K_0=zero order release rate constant

The plot of % drug release versus time is linear.

First order release model

The release rate data are fitted to the following equation

$$\ln (100-Q) = \ln 100 - k_1 t$$

Where, Q= percent drug release at time t

K_1= first order release rate constant

The plot of log % drug release versus time is linear.

Higuchi's Release Model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$$Q= K_H t^{1/2}$$

Where, Q= percent drug release at time t

K_H= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

Korsmeyer-peppas release model:
The release rate data were fitted to the following equation

$$F = (M_t/M) = K_m t^n$$

Where, M_t = drug release at time t

M = total amount of drug in dosage form

F = fraction of drug release at time t

K_m = constant dependent on geometry of dosage form

n = diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swellable and Cylindrical Matrix). In this model, a plot of log (M_t/M) versus log (time) is linear.

Drug excipients interaction studies
FT-IR spectrum interpretation
IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}. The results shown in Figure No.4a and 4b.

RESULTS AND DISCUSSION
Standard Calibration curve of Cetylpyridinium:
It was found that the estimation of Cetylpyridinium by UV spectrophotometric method at λ_{max} 271 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.0636x + 0.0751.

EVALUATION OF CETYLPYRIDINIUM BUCCAL PATCHES
Physical appearance
All the Buccal patches were visually inspected for colour, clarity, flexibility.
Flatness
All the Buccal patches was found to be flat with out any foams.

The prepared Cetylpyridinium Buccal patches were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be with in the pharmacopeial limits.

The prepared Cetylpyridinium Buccal patches were evaluated for *In-vitro* permeation studies using dialysis membrane, Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile.

The kinetics of *In-vitro* permeation studies using dialysis membrane for F6 formulation was plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. And the n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

Table No.1: Formulations of Cetylpyridinium Buccal Patch

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Drug(mg)	40	40	40	40	40	40	40	40	40	40	40	40
2	Eudragit L100(mg)	200	250	300	-	-	-	-	-	-	150	150	-
3	$HPMCk_4M$(mg)	-	-	-	200	250	300	-	-	-	150	-	150
4	$HPMCk_{15}M$(mg)	-	-	-	-	-	-	200	250	300	-	150	150
5	Dichloromethane(ml)	8	8	8	8	8	8	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8	8	8	8	8	8	8
7	Propylene glycol(ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
8	Tween-80(ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Table No.2: Concentration and absorbance obtained for calibration curve of Cetylpyridinium in (pH 6.8)

S. No	Concentration (µg/ml)	Absorbance* (at 271 nm)
1	2	0.128
2	4	0.267
3	6	0.456
4	8	0.589
5	10	0.762
6	12	0.963

Table No.3: Evaluation of Buccal patch by physical methods

S.No	Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
1	F1	0.3569	20	45	7.98	3.77
2	F2	0.3520	25	65	25.05	9.2
3	F3	0.3470	27	57.5	13.09	5.16
4	F4	0.3496	24	60	15.63	5.66
5	F5	0.3460	30	67.5	11.73	4.87
6	F6	0.3517	32	92.5	19.65	12.67
7	F7	0.3478	40	101.7	9.42	3.43
8	F8	0.3437	37	85	10.87	4.72
9	F9	0.3503	34	55	16.44	6.62
10	F10	0.3532	29	62.5	13.08	6.17
11	F11	0.3546	26	85	20.63	7.94
12	F12	0.3503	31	82.5	15.73	6.55

Table No.4: Evaluation of Buccal patch by *In-vitro* permeation studies using dialysis membrane

S.No	Time (hrs)	% Drug release											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	1	9.05	15.1	10.1	9.49	10.9	20.2	17.5	12.0	11.1	12.7	10.0	20.4
2	2	13.3	19.8	12.8	11.3	19.6	27.8	21.9	17.5	13.0	17.9	12.5	25.4
3	4	14.6	28.3	21.5	22.6	24.9	42.8	33.5	23.4	23.3	27.4	23.6	33.0
4	6	21.9	34.1	25.9	32.3	31.2	53.5	40.0	30.9	33.4	32.7	30.9	41.7
5	8	32.7	41.1	33.4	43.9	38.0	66.3	46.5	48.1	52.7	50.6	36.7	47.9
6	10	40.4	50.1	44.5	56.3	50.3	82.0	64.2	60.0	66.4	63.0	45.9	63.0
7	12	54.2	65.8	56.7	69.4	65.9	94.7	91.9	78.7	79.1	74.8	56	80.9

Table No.5: Kinetics of *In-vitro* permeation studies using dialysis membrane

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain	Release rate (cumulative % release/t)	1/cum % release	Peppas log Q/100	% drug remain	Q01/3	Qt1/3	Q01/3 - Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
20.2356	1	1.000	1.306	0.000	1.902	20.236	0.0494	-0.694	79.7644	4.642	4.305	0.337
27.80759	2	1.414	1.444	0.301	1.858	13.904	0.0360	-0.556	72.19241	4.642	4.164	0.478
42.87958	4	2.000	1.632	0.602	1.757	10.720	0.0233	-0.368	57.12042	4.642	3.851	0.790
53.59293	6	2.449	1.729	0.778	1.667	8.932	0.0187	-0.271	46.40707	4.462	3.594	1.048
66.38743	8	2.828	1.822	0.903	1.527	8.270	0.0151	-0.178	33.61257	4.642	3.227	1.414
82.0877	10	3.162	1.914	1.000	1.253	8.209	0.0122	-0.086	17.9123	4.642	2.616	2.025
94.7055	12	3.464	1.976	1.079	0.724	7.892	0.0106	-0.024	5.294503	4.642	1.743	2.899
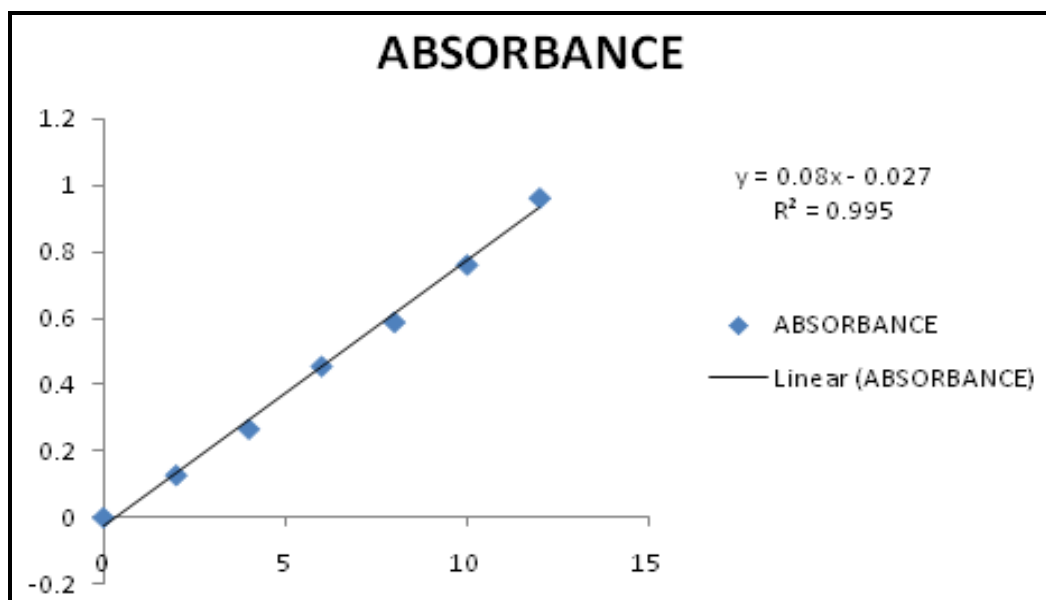
Figure No.1: Standard graph of Cetylpyridinium in pH 6.8 Phosphate buffer
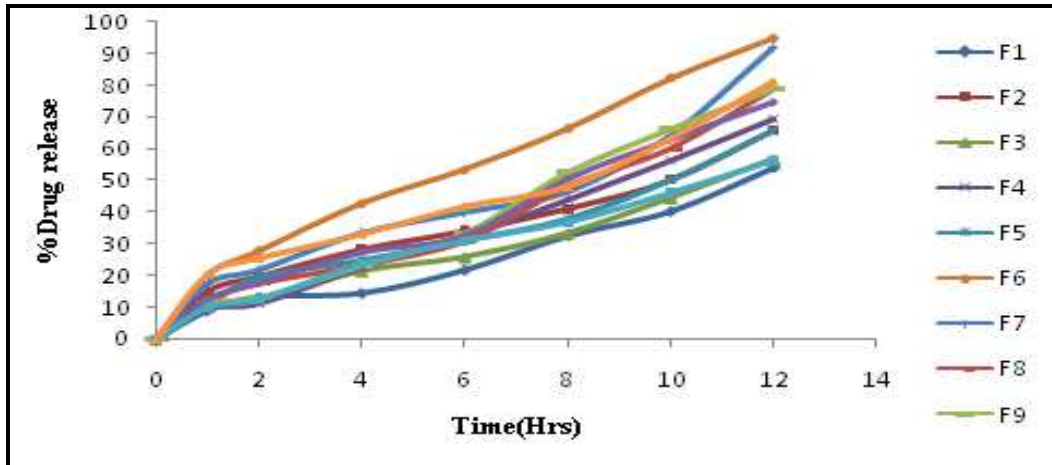
Figure No.2: Release profile of *In-vitro* permeation studies using dialysis membrane
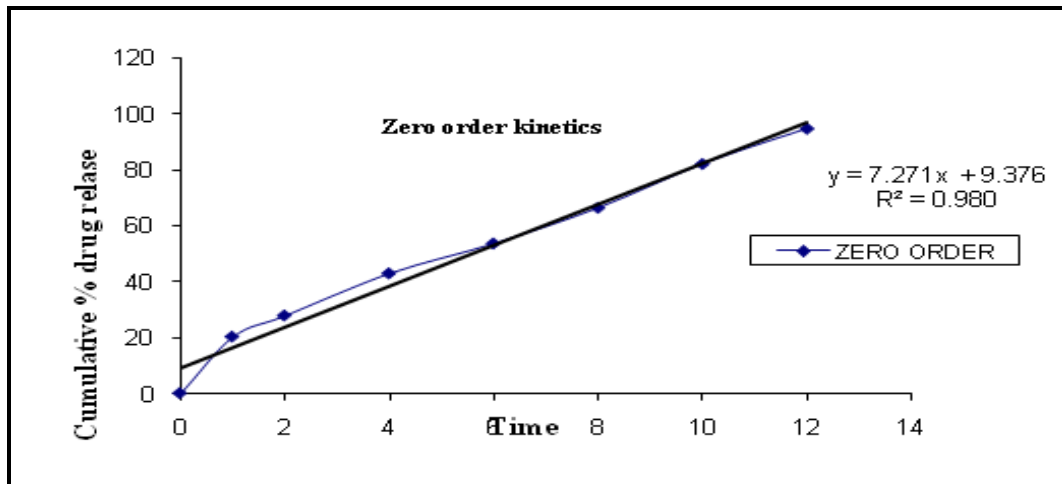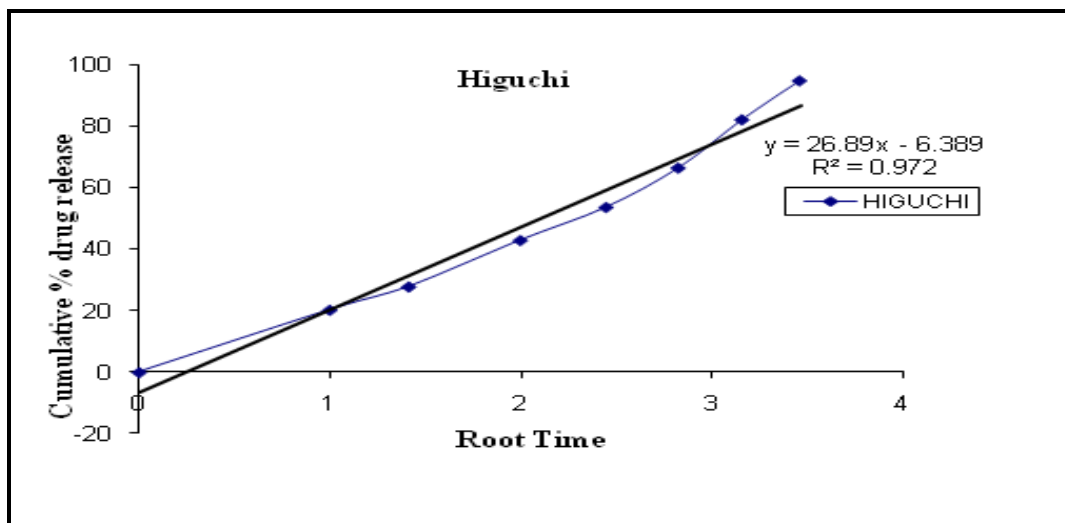

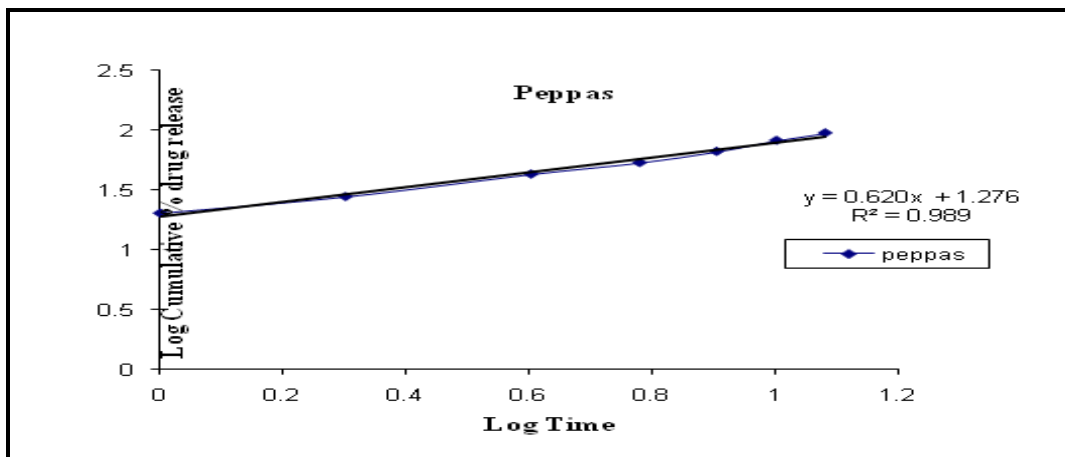**Figure No.3a: Zero order kinetics**

Figure No.3b: Higuchi plot

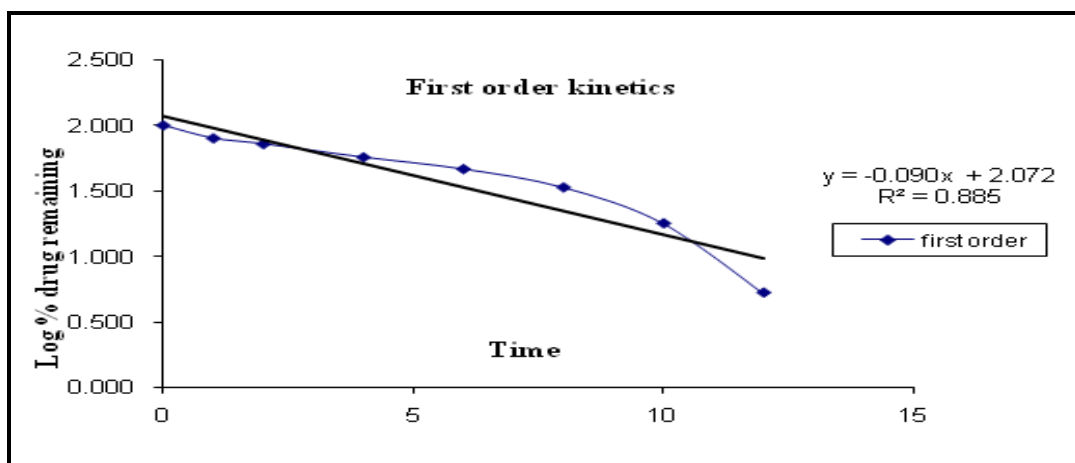**Figure No.3c: Peppas plot**

Figure No.3d: First order kinetics
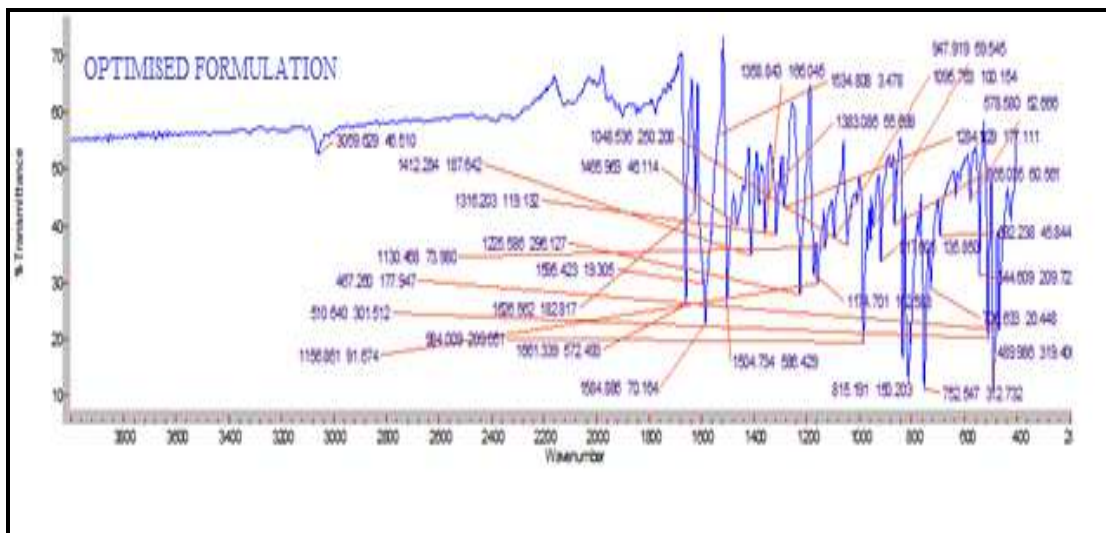

Figure No.4a: FTIR spectrum of pure drug

Figure No.4b: FTIR spectrum of optimized formulation

CONCLUSION

In present study buccal drug delivery of Cetylpyridinium was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of buccal patches was developed by using polymers Eudragit-L100, HPMC K4M and HPMC K15M. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F12, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be with in the pharmacopeial limits, *in vitro* drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest
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